Centers for Disease Control and Prevention
Epidemiology Program Office
Case Studies in Applied Epidemiology
No. 912-303

Suspected Legionnaires' Disease in Bogalusa

Instructor's Guide

Learning Objectives
After completing this case study, the participant should be able to:

- ☐ Discuss the relationship between and roles of state-based and Atlanta-based EIS officers in a field investigation;
- ☐ Develop an epidemiologic case definition;
- ☐ Calculate power for a case-control study;
- ☐ Describe different sources of controls for a community-based outbreak.

This case study is based on an investigation conducted in 1989 by the Louisiana Department of Health and Hospitals and the Centers for Disease Control. This case study was developed in 1991 by Frank Mahoney, John Horan, and Richard Dicker. The current (1998) version was updated and edited by Richard Dicker, with comments and input from the 1998 EIS Summer Course instructors.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

PART I

On October 31, 1989, the Louisiana Department of Health and Hospitals (LDHH) was notified by two physicians in Bogalusa, Louisiana that over 50 cases of acute pneumonia had occurred among local residents. Most cases had occurred within a 3-week interval from mid- to late October. All cases had occurred in adults. Six persons had died.

Clinical histories from several patients suggested that the illness may have been Legionnaires' disease, caused by infection with the bacterium *Legionella pneumophila.*

You are the EIS Officer assigned to the Epidemiology Section of the LDHH.

Question 1: If you had taken this call, what additional information would you request over the telephone?

Answer 1
You want to begin to characterize this possible outbreak by describing the what, who, when, where, and why. You will also want to know some administrative, logistical or operational information.

DIAGNOSIS-RELATED ("What")
- How certain is the diagnosis? (Could it be a new doc in town who is overdiagnosing?)
- Any lab results available? (If positive lab results, could it be lab error?)

DESCRIPTIVE EPIDEMIOLOGY ("Who," "When," "Where")
- What is the denominator for the observed cases? (What are the referral patterns? Have they changed?)
- What is the background incidence of pneumonia? of legionellosis (particularly, number of cases in same month last year)? Has a similar cluster been noted before?
- Any additional time/place/person (age, etc.) information available?
- Case-finding issues: Might this be the tip of the iceberg? Are cases occurring in other hospitals or areas? How active has case finding been?

POSSIBLE CAUSES ("Why")
- Are the cases related in any obvious way? Do the case-patients know each other? Do they work or convene together?
- Are there cooling towers in the town? (a known risk factor for legionellosis)
- Do they appear to have community-acquired or hospital-acquired disease?
- What do the locals or the patients themselves think is going on?

ADMINISTRATIVE / OPERATIONAL / LOGISTICAL
- Has the local health department been notified / involved?
- What has been done already? To what effect?
- Who has already been involved in the investigation?
- What resources are available locally? (lab, epi, etc.)
- Does the public / media know?
- Who else should know? (for example, neighboring counties or states)

Serologic testing of several patients during the initial phase of illness had been negative for *Legionella* antibody. No sputum specimens had been collected for Legionnaires' testing, since the hospital's laboratory was not able to perform the tests.

Question 2: In general, besides a true outbreak, what else can account for a sudden increase in the number of cases of a particular disease to be reported to a health department?

Answer 2

Artifactual reasons include:

- changes in local reporting procedures (e.g., easier reporting, such as change to active from passive
- changes in case definition (cf: AIDS)
- increased awareness / interest because of local or national awareness
    - by the public (will seek medical care)
    - by the doctor (more likely to diagnose)
    - new laboratory test available (more sensitive, therefore more diagnoses)
- improvements in diagnostic skill (new doc?) or procedures
- Increased testing (e.g., new policy in a clinic or HMO to begin testing specimens from more patients with acute illness)
- Increased reporting (new physician or clinic or change in patient referral pattern)
- outbreak of similar disease, misdiagnosed as disease of interest
- duplicate reports
- laboratory error

Depending on perspective, can be considered "real" or artifactual:

- change in denominator - influx of tourists (Cape Cod), refugees, migrant farmers, etc.

Question 3: Assuming you will depart for Bogalusa to conduct a field investigation, what sorts of preparations do you need to make?

Answer 3

INVESTIGATION-RELATED

- Gain scientific knowledge
    - Discuss with supervisor or someone else knowledgeable about pneumonia/legionellosis epi and about field investigations;
    - Review applicable literature, assemble useful references and sample questionnaires.
- Gather supplies and equipment
    - Consult with laboratory staff to ensure that investigator is taking the proper laboratory material and knows the proper collection, storage, and transportation techniques.
    - Find portable computer, dictaphone, camera, and other supplies as needed.

ADMINISTRATIVE

- Travel, cash advance, credit cards, etc.
- Personal matters

EXPECTED ROLE IN THE FIELD

- Agree on the investigator's role (i.e., is investigator expected to lead the investigation, or provide consultation to the local staff who will conduct the investigation, or simply lend a hand to the local staff?)
- Who will the local contacts will be? Agree on time and place to meet with local officials and contacts upon arrival.

To refresh their knowledge of Legionnaires' disease, the investigators turned to **Control of Communicable Diseases in Man, fifteenth edition**, the edition available at the time. The following is abstracted from that handbook:

Legionnaires' disease, or legionelllosis, is characterized by pneumonia caused by the bacterium Legionella pneumophila. The incubation period ranges from 2 to 10 days. The disease often begins with anorexia [loss of appetite]*, malaise* [fatigue and overall sense of poor well-being]*, myalgias* [muscle aches and soreness]*, and headache, followed by rapidly rising fever and chills. Chest X-rays typically show patchy areas of consolidation. The diagnosis is confirmed by:*

1) *isolation of the organism on special media; or*
2) *demonstration by immunofluorescent stain of involved tissue or respiratory secretions; or*
3) *fourfold or greater increase in titers between acute and convalescent phase serum samples, or*
4) *a single high titer (>1:256) in a patient with a compatible clinical course.*

[In 1999, the diagnosis may be made by detecting antigens to serogroup 1 in urine.]

Cases of legionnaires' disease occur sporadically [individually] *and in outbreaks. The reservoir of the causative organism is primarily aqueous, such as hot water systems, air conditioning cooling towers, and evaporator condensers. The mode of transmission is airborne via aerosol-producing devices. Risk factors for serious illness include increasing age, especially in smokers; diabetes, chronic lung disease, renal disease or cancer; or immunocompromised patients. The usual male-to-female ratio is about 2.5:1.*

Bogalusa is located in Washington Parish and has a population of about 16,000 persons. The largest employer is a paper mill located in the center of town adjacent to the main street. The paper mill includes five prominent industrial cooling towers. The mill also has three paper machines that emit large volumes of aerosol along the main street in town. Many persons suspected the cooling towers and/or paper machines to be the cause of the outbreak, since they were prominent sources of outdoor aerosols. Attention was also directed at a few public buildings with cooling towers, since they were potential sources of indoor aerosol.

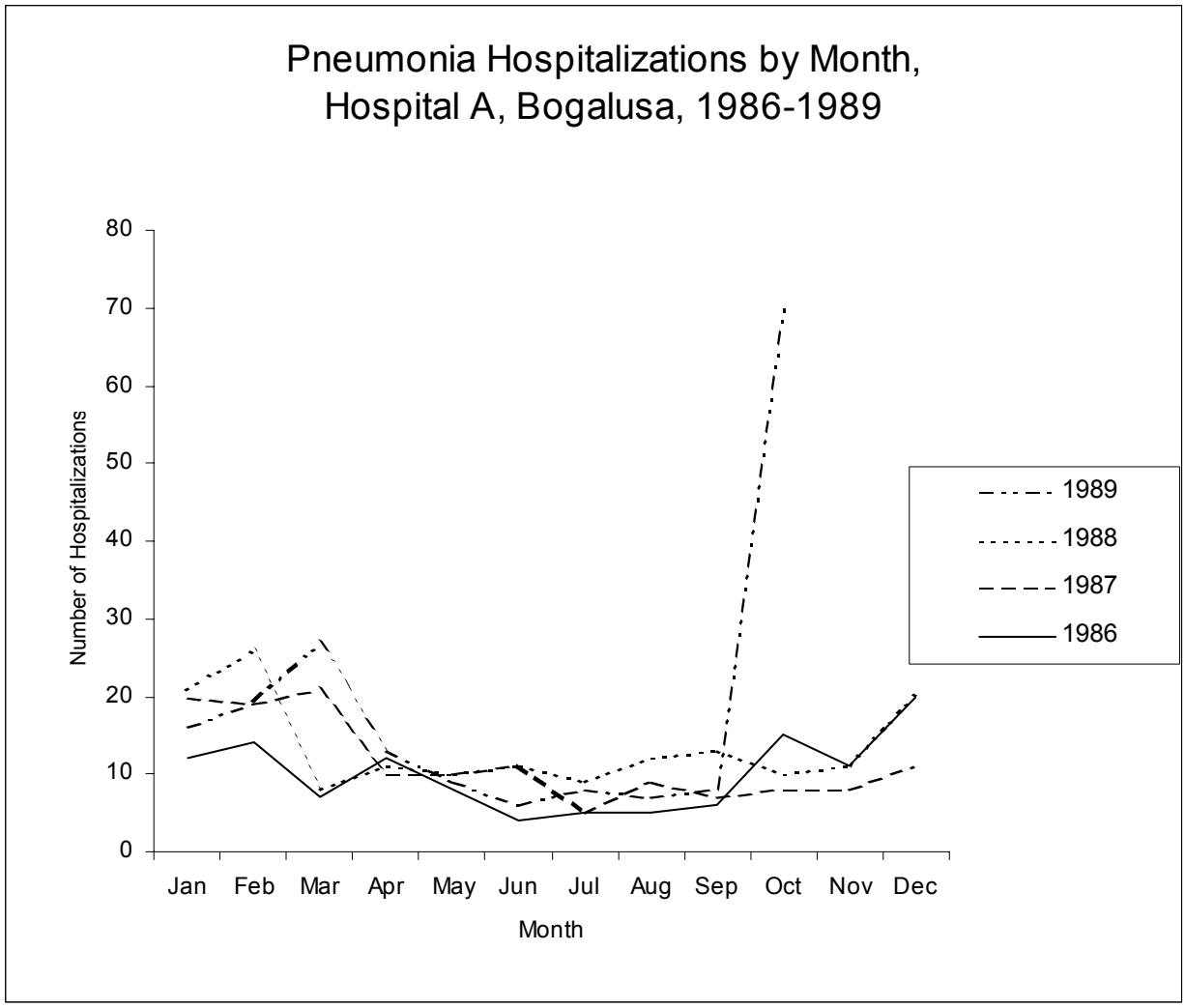
Bogalusa is served by a 98-bed private hospital (hospital A) and a 60-bed public hospital (hospital B). Three additional hospitals are located in the surrounding parish. All of the reported cases were from Hospital A.

The number of patients discharged with a diagnosis of pneumonia at Hospital A since January 1986 is shown in Table 1. Between January 1986 and September 1989, only one pneumonia patient had been diagnosed as having Legionnaires' disease.

Table 1. Number of Patients with a Diagnosis of Pneumonia Discharged from Hospital A by Month, 1986-1989

	1986	1987	1988	1989
January	12	20	21	16
February	14	19	26	19
March	7	21	8	27
April	12	10	11	13
May	8	10	10	9
June	4	11	11	6
July	5	5	9	8
August	5	9	12	7
September	6	7	13	8
October	15	8	10	70
November	?	8	11	
December	?	11	20	
Total	88	139	162	183

Instructor's Note: Shown is a graph of the data in Table 1.



Review of charts of pneumonia patients at Hospital A during October revealed that many patients had fever, weakness, lethargy, and mental confusion. Some patients had a dry cough, and several reported having watery diarrhea. Chest X-rays showed patchy infiltrates indicative of pneumonia. Most patients were residents of Bogalusa or the surrounding areas of Washington Parish.

Question 4: Develop a case definition for this outbreak.

Answer 4
Instructor's note 1: Break class into groups of 3-4 to develop a case definition.

Instructor's note 2: Remind participants that case definition should include four components: clinical info, time, place, and person. Often, field investigators create a hierarchy of case definitions based on certainty of the diagnosis, e.g., confirmed vs. suspect.

One reasonable case definition is:
Clinical: **confirmed**: laboratory confirmation as described in CCDM
possible: hospitalized with "physician diagnosis of suspect legionnaires' disease," with no other documented agent for pneumonia
Time: date of onset after September 1, 1989 (or October 1)
Place: resident or visitor of Washington Parish or adjacent parishes
Person: resident or visitor of Washington Parish or adjacent parishes

In this investigation, the primary objective is to find the cause rather than to characterize the extent of the outbreak. Therefore, a more limiting (specific) rather than a more inclusive (sensitive) case definition is preferred, to ensure that all your cases have the same disease.

Question 5: Would you look for additional cases? How? Do you need to find every case?

Answer 5
Yes. From a public health point of view, it is important to determine the extent of the outbreak.

- Check the other area hospitals, labs, physicians (especially infectious disease specialists and pulmonologists). An advantage of talking to the clinical community is to get them to appropriately test people with pneumonia, and to report those who test positive for legionnaires' disease.
- Talk to case-patients – they may know others who are ill.
- Use the media to publicize (a "double-edged sword" -- may stimulate case-finding, but may cause panic or over-reporting)

Do you need to find every case? (i.e., Do you need a more sensitive case definition and case-finding approach?) This would be helpful for characterizing the full extent of the outbreak, but is not necessary for establishing the source and mechanism of the outbreak. Analytic results are likely to be affected only if strong selection bias of some sort (i.e., if detection is related to the exposure we're trying to study). Also, time and resources are often limited and must be taken into consideration.

Question 6: You are asked to address the hospital staff. What might you tell them?

Answer 6
You may have several objectives in mind when you talk to the medical staff. You want to get their support, cooperation, and assistance. You also want to make sure they can recognize (diagnose) and appropriately treat patients with Legionnaires' disease. So you might want to cover:
- Clinical features of Legionnaires' disease
- How to diagnose (and what specimens are needed)
- A little epidemiology (because we're epidemiologists!)
- Why its important to report a case and how to report
- How to treat (erythromycin)
- What you're planning to do to (describe your epi investigation plan)
- What you know to date
- Why you need their help (access to charts and patients- verify case definition, enroll in study, etc.)

If you were coming from CDC, you should try to make this a joint presentation with the local health department staff, since they will remain (and will need to work with these clinicians) after you leave.

Other hospital staff may also be concerned with how the disease spreads, and whether they are at risk by working at the hospital!

Discussions were held among staff of the LDHH and the CDC. LDHH felt capable of conducting the epidemiologic investigation, but requested assistance with laboratory support. CDC proposed that an EIS Officer from Atlanta assist in the epidemiologic investigation and that CDC provide laboratory support. The field investigation team arrived in Bogalusa on November 8.

Question 7: Given that Louisiana had its own epidemiologists including a field EIS officer, what issues should be decided up front?

Answer 7
Issues generally relative to roles and responsibilities, i.e., who is responsible for what:
- who is in charge and providing overall direction (including which supervisor has lead responsibility)
- who is responsible for what in terms of the investigation and data analysis
- who will take the lead on writing up the *MMWR* and final report [authorship], if appropriate
- who is responsible for communicating with the public and hospital staff
- who is responsible for dealing with the laboratory
- etc.

PART II

Discussions were held among staff of the Louisiana health department and the CDC. The health department felt capable of conducting the epidemiologic investigation, but requested assistance with laboratory support. A second EIS Officer was sent from Atlanta to assist in the investigation, and CDC provided laboratory support. The field investigation team arrived in Bogalusa on November 8.

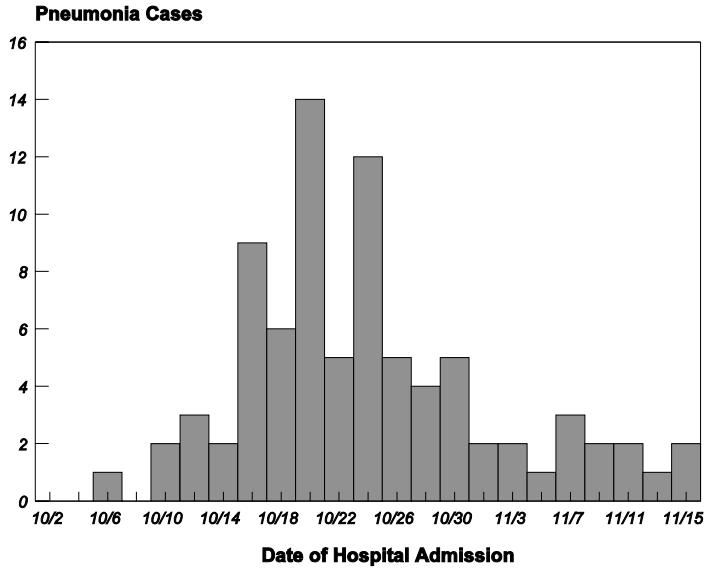
The investigators set up active surveillance for case-finding at all five local hospitals in the Bogalusa area. In addition, they used a standard questionnaire to abstract information from the medical records of all persons admitted or discharged with a diagnosis of pneumonia, respiratory distress, or possible Legionnaires' disease (LD) since October 1, 1989.

Investigators defined a possible case of LD was as illness in a resident or visitor of Washington Parish, $20 years of age, admitted to one of the 5 local hospitals after October 1, 1989, with an X-ray consistent with pneumonia. A confirmed case had to meet the criteria for a possible case, plus have laboratory evidence of LD (four-fold rise in antibody titer, a single convalescent antibody titer $ 1:256, positive urine antigen test, positive sputum culture, or positive biopsy).

By November 19, investigators had identified 83 patients who met the definition of possible LD (Figure 1). Fourteen of these patients had died without Legionella testing. Of the 83, 65% were female, and 28% were African-American. About three-fourths of the case-patients were residents of Bogalusa; about half (41) resided on the east side of town. Most case-patients had been admitted to the hospital in mid-October; few if any new cases were occurring in mid-November (Figure 1). To date, no sputum culture had shown growth for LD or other pathogens.

Before designing the analytic portion of the investigation, the investigators considered their leading hypotheses.

Figure 1. Number of cases of pneumonia by date of hospital admission, Bogalusa, 1989



Question 8: How does one generate plausible hypotheses to test in this type of investigation?

Answer 8
- Ask what the local public health (and clinical) folks think
- What do the case-patients or their families think?
- Subject matter knowledge: What are the known causes, reservoirs, modes of transmission for the disease? ("Round up the usual suspects!")
- From the overall patterns seen in the descriptive epidemiology
- From the exceptions or outliers in the descriptive epidemiology

At this point in the investigation, the leading hypothesis was outdoor exposure to cooling towers, primarily because previous studies had demonstrated the role of cooling towers as sources of the *Legionella pneumophila* in other outbreaks, and there were several such towers in the town. However, rather than jumping to conclusions based on this information alone, investigators began to compile a list of retail stores and other establishments which were frequently mentioned by some of the case-patients who had been interviewed. The investigators also noted the unusual preponderance of female cases.

Question 9: In this setting, what type of study would you use to test your hypotheses?

Answer 9
For at least two reasons, a case-control study is the preferred and most efficient method for examining the hypotheses in this outbreak:

- Through surveillance, data are available for a portion of the total number of cases (referred to as a "case series"), but you don't know what specific exposure may be causing the disease. Since exposure is unknown, the study must start with disease status. In a case-control study design, a comparison group of individuals without disease can be used to evaluate the relationship between the disease and multiple possible exposures.

- The objective of this investigation is to rapidly determine the source of the outbreak in order to institute control measures – the case-control study can be conducted quickly.

PART III

The investigators decided to conduct a case-control study to test their hypotheses. Sixty-six persons met the case definition for a possible case and were still alive. Laboratory results had come back confirming Legionnaires' disease in 15 of these patients, and ruling out Legionnaires' disease in 10. Laboratory results for the remainder were pending.

Question 10: What case definition would you use for the case-control study?

Answer 10
Two separate concerns are power and misclassification. Because a substantial number of possible cases are coming back as non-LD, we'd prefer to use only confirmed cases. Using possible cases will result in misclassification of some non-cases as cases. However, by cutting down on the number of useable cases, we reduce the power of our study (the ability to detect a statistically significant association, if indeed disease is related to the exposure). Bottom line: in epidemiology, validity is more important than power.

Question 11: How does one go about determining an appropriate number of controls? What factors go into this determination?

Answer 11
Sample size / power calculations, as well as resource limitations and other practical considerations. Power calculations are based on:
- the number of cases
- the number of controls per case
- the strength of the association
- the proportion of exposed non-cases in the population
- the desired level of statistical significance

Question 12: What are some possible sources of controls?

Answer 12
First, review the concept that controls should be drawn from the same population and be as similar as possible to cases, except for the presence of infection/disease (i.e., a control should be someone who, if they became ill, would be counted as a case in your study]. Then consider possible sources:
- medical: physicians' offices, hospital, etc.
- acquaintances: family members, neighbors, friends, coworkers
- community: population-based (e.g., by telephone random-digit dialing or population-based survey)

PART IV

The investigators decided to select controls from office records of physicians who admitted the cases.

Before conducting a study of a small number of cases, it is often useful to calculate the power or ability of a study to detect, at a statistically significant level, a particular odds ratio or difference between cases and controls.

The statistical power of a case-control study is influenced by 5 factors:

1. **n**, the number of cases;
2. **c**, the number of controls per case;
3. **OR**, the odds ratio in the source population worth detecting;
4. **p_0**, the proportion of exposed non-cases in the source population;
5. **α ("alpha")**, the desired level of significance. The corresponding 2-tailed **Z_α** from the normal distribution is used in the formulas, e.g., for α = 0.05, Z_α = 1.96.

The calculation of a study's power involves two steps. First, we calculate **Z_β** ("Z-beta"). Second, we determine the POWER, which is equal to 1-β, by looking up in a table of standard normal cumulative probabilities the cumulative probability associated with that Z_β.

A formula for calculating Z_β, with n cases and c controls per case, is given by:

$$Z_\beta = [n(p_1 - p_0)^2 / pq(1 + 1/c)]^{½} - Z_\alpha$$

where $p_1 = p_0OR / [1 + p_0(OR - 1)]$ = proportion of cases exposed

$p = (p_1 + cp_0) / (1 + c)$ = proportion of all subjects exposed

and $q = 1 - p$

EXAMPLE

Suppose you were designing the case-control study to test the association between exposure to a particular water tower and Legionnaires' disease. You figure that you could enroll about 50 of the cases, and that about 14% of the town's population is exposed to the water tower in question. You might be able to afford (in terms of time and resources) to enroll 3 controls per case, and you were indoctrinated that α is always 0.05. Calculate the study's power to detect a true odds ratio of 2.0.

Given: n = 50, c = 3, p_0 = 0.14, and OR = 2.0

$p_1 = (0.14)(2.0) / [1 + 0.14(2.0 - 1)] = 0.246$

$p = [0.246 + (3)(0.14)] / (1 + 3) = 0.167$

$q = 1 - 0.167 = 0.834$

$Z_\beta = [50(0.246 - 0.14)^2 / (0.167)(0.834)(1+ 1/3)]^{½} - 1.96 = -0.221$

POWER (1-β) = cumulative probability of -0.221 = 0.413

In other words, a study of 50 cases and 150 controls would be expected a priori (that is, based on the estimated exposure to the water tower of 14%) to have an approximately 41% chance of detecting a statistically significant association in the study, if the underlying association between water tower exposure and Legionnaires' disease in the population were 2.0.

Question 13: Using the formulas above, calculate the power of the study to detect an odds ratio of 2, 3, or 4 at an alpha of 0.05 using 2 controls per case, as indicated in the table below.

Table 2. Statistical Power of a Case-Control Study with n=50, p_0=0.14, and α=0.05, for different control-to-case ratios and underlying associations

	Control-to-Case Ratio				
	1	2	3	4	10
OR = 2 (p_1 = 0.246)	0.25		0.41 (example)	0.45	0.51
OR = 3 (p_1 = 0.328)	0.59		0.82	0.84	0.88
OR = 4 (p_1 = 0.394)	0.84		0.96	0.97	0.98

Answer 13

Given: n = 50, c = 2, p_0 = 0.14, and OR = 2.0, p_1 = 0.246

p = [0.246 + (3 x 0.14)] / (1 + 2) = 0.1752, q = 1 - 0.1752 = 0.8248

$Z_\beta = [50(0.246 - 0.14)^2 / (0.1752)(0.8248)(1+ ½)]^{½} - 1.96 =$ **-0.356**, corresponds to Power = **36%**

For OR = 3, p_1 = 0.328, p = [0.328 + (3 x 0.14)] / (1 + 2) = 0.2027, q = 1 - 0.2027 = 0.7973

$Z_\beta = [50(0.328 - 0.14)^2 / (0.2027)(0.7973)(1+ ½)]^{½} - 1.96 =$ **0.742**, corresponds to Power = **77%**

For OR = 4, p_1 = 0.394, p = [0.394 + (3 x 0.14)] / (1 + 2) = 0.2248, q = 1 - 0.2248 = 0.7752

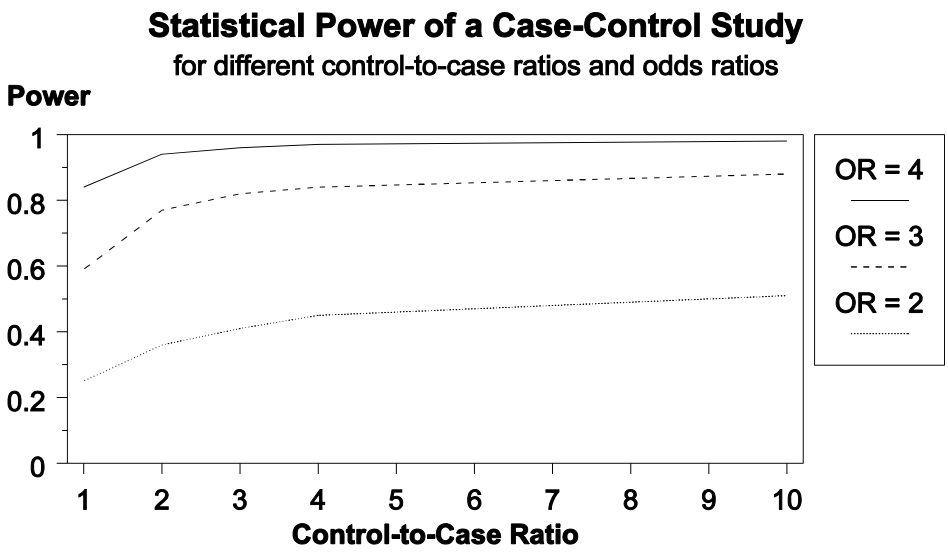
$Z_\beta = [50(0.394 - 0.14)^2 / (0.2248)(0.7752)(1+ ½)]^{½} - 1.96 =$ **1.55**, corresponds to Power = **94%**

	Control-to-Case Ratio				
	1	2	3	4	10
OR = 2 (p_1 = 0.246)	0.25	**0.36**	0.41 (example)	0.45	0.51
OR = 3 (p_1 = 0.328)	0.59	**0.77**	0.82	0.84	0.88
OR = 4 (p_1 = 0.394)	0.84	**0.94**	0.96	0.97	0.98

Question 14: Discuss the pattern illustrated by the power estimates in the table.

Answer 14

a. Given a fixed number of cases, the power of a study is a function of the number of controls and the association one is trying to detect. All else being equal, a study always has more power to detect a stronger association than a weaker one.
b. Given 50 cases, the study has poor power to detect an odds ratio of 2, even with 10 controls per case. However, the study has very good power to detect an odds ratio of 4, even with only one control per case.
c. The table illustrates the general rule that very little power is gained by increasing the control-to-case ratio beyond three or four.



STANDARD NORMAL CUMULATIVE PROBABILITIES, Page 1 of 2

Z	0.00	0.01	0.02	0.03	0.04	0.05	0.06	0.07	0.08	0.09
-3.8	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
-3.7	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
-3.6	0.0002	0.0002	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
-3.5	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002
-3.4	0.0003	0.0003	0.0003	0.0003	0.0003	0.0003	0.0003	0.0003	0.0003	0.0002
-3.3	0.0005	0.0005	0.0005	0.0004	0.0004	0.0004	0.0004	0.0004	0.0004	0.0003
-3.2	0.0007	0.0007	0.0006	0.0006	0.0006	0.0006	0.0006	0.0005	0.0005	0.0005
-3.1	0.0010	0.0009	0.0009	0.0009	0.0008	0.0008	0.0008	0.0008	0.0007	0.0007
-3.0	0.0013	0.0013	0.0013	0.0012	0.0012	0.0011	0.0011	0.0011	0.0010	0.0010
-2.9	0.0019	0.0018	0.0018	0.0017	0.0016	0.0016	0.0015	0.0015	0.0014	0.0014
-2.8	0.0026	0.0025	0.0024	0.0023	0.0023	0.0022	0.0021	0.0021	0.0020	0.0019
-2.7	0.0035	0.0034	0.0033	0.0032	0.0031	0.0030	0.0029	0.0028	0.0027	0.0026
-2.6	0.0047	0.0045	0.0044	0.0043	0.0041	0.0040	0.0039	0.0038	0.0037	0.0036
-2.5	0.0062	0.0060	0.0059	0.0057	0.0055	0.0054	0.0052	0.0051	0.0049	0.0048
-2.4	0.0082	0.0080	0.0078	0.0075	0.0073	0.0071	0.0069	0.0068	0.0066	0.0064
-2.3	0.0107	0.0104	0.0102	0.0099	0.0096	0.0094	0.0091	0.0089	0.0087	0.0084
-2.2	0.0139	0.0136	0.0132	0.0129	0.0125	0.0122	0.0119	0.0116	0.0113	0.0110
-2.1	0.0179	0.0174	0.0170	0.0166	0.0162	0.0158	0.0154	0.0150	0.0146	0.0143
-2.0	0.0228	0.0222	0.0217	0.0212	0.0207	0.0202	0.0197	0.0192	0.0188	0.0183
-1.9	0.0287	0.0281	0.0274	0.0268	0.0262	0.0256	0.0250	0.0244	0.0239	0.0233
-1.8	0.0359	0.0351	0.0344	0.0336	0.0329	0.0322	0.0314	0.0307	0.0301	0.0294
-1.7	0.0446	0.0436	0.0427	0.0418	0.0409	0.0401	0.0392	0.0384	0.0375	0.0367
-1.6	0.0548	0.0537	0.0526	0.0516	0.0505	0.0495	0.0485	0.0475	0.0465	0.0455
-1.5	0.0668	0.0655	0.0643	0.0630	0.0618	0.0606	0.0594	0.0582	0.0571	0.0559
-1.4	0.0808	0.0793	0.0778	0.0764	0.0749	0.0735	0.0721	0.0708	0.0694	0.0681
-1.3	0.0968	0.0951	0.0934	0.0918	0.0901	0.0885	0.0869	0.0853	0.0838	0.0823
-1.2	0.1151	0.1131	0.1112	0.1093	0.1075	0.1056	0.1038	0.1020	0.1003	0.0985
-1.1	0.1357	0.1335	0.1314	0.1292	0.1271	0.1251	0.1230	0.1210	0.1190	0.1170
-1.0	0.1587	0.1562	0.1539	0.1515	0.1492	0.1469	0.1446	0.1423	0.1401	0.1379
-0.9	0.1841	0.1814	0.1788	0.1762	0.1736	0.1711	0.1685	0.1660	0.1635	0.1611
-0.8	0.2119	0.2090	0.2061	0.2033	0.2005	0.1977	0.1949	0.1922	0.1894	0.1867
-0.7	0.2420	0.2389	0.2358	0.2327	0.2296	0.2266	0.2236	0.2206	0.2177	0.2148
-0.6	0.2743	0.2709	0.2676	0.2643	0.2611	0.2578	0.2546	0.2514	0.2483	0.2451
-0.5	0.3085	0.3050	0.3015	0.2981	0.2946	0.2912	0.2877	0.2843	0.2810	0.2776
-0.4	0.3446	0.3409	0.3372	0.3336	0.3300	0.3264	0.3228	0.3192	0.3156	0.3121
-0.3	0.3821	0.3783	0.3745	0.3707	0.3669	0.3632	0.3594	0.3557	0.3520	0.3483
-0.2	0.4207	0.4168	0.4129*	0.4090	0.4052	0.4013	0.3974	0.3936	0.3897	0.3859
-0.1	0.4602	0.4562	0.4522	0.4483	0.4443	0.4404	0.4364	0.4325	0.4286	0.4247
0.0	0.5000	0.4960	0.4920	0.4880	0.4840	0.4801	0.4761	0.4721	0.4681	0.4641

* Use this table to find the power which corresponds to Z_β. For a given value of Z_β (say, -0.221), find that value to 1 decimal place in the left-most column (-0.2). The power will be in the -0.2 row. Now find the second decimal of your Z_β across the top row (0.02). The power is in that column. The power is at the intersection of the row and column you've identified (for -0.02 and 0.02, power = 0.41, or 41%).

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Z	0.00	0.01	0.02	0.03	0.04	0.05	0.06	0.07	0.08	0.09
0.1	0.5398	0.5438	0.5478	0.5517	0.5557	0.5596	0.5636	0.5675	0.5714	0.5753
0.2	0.5793	0.5832	0.5871	0.5910	0.5948	0.5987	0.6026	0.6064	0.6103	0.6141
0.3	0.6179	0.6217	0.6255	0.6293	0.6331	0.6368	0.6406	0.6443	0.6480	0.6517
0.4	0.6554	0.6591	0.6628	0.6664	0.6700	0.6736	0.6772	0.6808	0.6844	0.6879
0.5	0.6915	0.6950	0.6985	0.7019	0.7054	0.7088	0.7123	0.7157	0.7190	0.7224
0.6	0.7257	0.7291	0.7324	0.7357	0.7389	0.7422	0.7454	0.7486	0.7517	0.7549
0.7	0.7580	0.7611	0.7642	0.7673	0.7704	0.7734	0.7764	0.7794	0.7823	0.7852
0.8	0.7881	0.7910	0.7939	0.7967	0.7995	0.8023	0.8051	0.8078	0.8106	0.8133
0.9	0.8159	0.8186	0.8212	0.8238	0.8264	0.8289	0.8315	0.8340	0.8365	0.8389
1.0	0.8413	0.8438	0.8461	0.8485	0.8508	0.8531	0.8554	0.8577	0.8599	0.8621
1.1	0.8643	0.8665	0.8686	0.8708	0.8729	0.8749	0.8770	0.8790	0.8810	0.8830
1.2	0.8849	0.8869	0.8888	0.8907	0.8925	0.8944	0.8962	0.8980	0.8997	0.9015
1.3	0.9032	0.9049	0.9066	0.9082	0.9099	0.9115	0.9131	0.9147	0.9162	0.9177
1.4	0.9192	0.9207	0.9222	0.9236	0.9251	0.9265	0.9279	0.9292	0.9306	0.9319
1.5	0.9332	0.9345	0.9357	0.9370	0.9382	0.9394	0.9406	0.9418	0.9429	0.9441
1.6	0.9452	0.9463	0.9474	0.9484	0.9495	0.9505	0.9515	0.9525	0.9535	0.9545
1.7	0.9554	0.9564	0.9573	0.9582	0.9591	0.9599	0.9608	0.9616	0.9625	0.9633
1.8	0.9641	0.9649	0.9656	0.9664	0.9671	0.9678	0.9686	0.9693	0.9699	0.9706
1.9	0.9713	0.9719	0.9726	0.9732	0.9738	0.9744	0.9750	0.9756	0.9761	0.9767
2.0	0.9772	0.9778	0.9783	0.9788	0.9793	0.9798	0.9803	0.9808	0.9812	0.9817
2.1	0.9821	0.9826	0.9830	0.9834	0.9838	0.9842	0.9846	0.9850	0.9854	0.9857
2.2	0.9861	0.9864	0.9868	0.9871	0.9875	0.9878	0.9881	0.9884	0.9887	0.9890
2.3	0.9893	0.9896	0.9898	0.9901	0.9904	0.9906	0.9909	0.9911	0.9913	0.9916
2.4	0.9918	0.9920	0.9922	0.9925	0.9927	0.9929	0.9931	0.9932	0.9934	0.9936
2.5	0.9938	0.9940	0.9941	0.9943	0.9945	0.9946	0.9948	0.9949	0.9951	0.9952
2.6	0.9953	0.9955	0.9956	0.9957	0.9959	0.9960	0.9961	0.9962	0.9963	0.9964
2.7	0.9965	0.9966	0.9967	0.9968	0.9969	0.9970	0.9971	0.9972	0.9973	0.9974
2.8	0.9974	0.9975	0.9976	0.9977	0.9977	0.9978	0.9979	0.9979	0.9980	0.9981
2.9	0.9981	0.9982	0.9982	0.9983	0.9984	0.9984	0.9985	0.9985	0.9986	0.9986
3.0	0.9987	0.9987	0.9987	0.9988	0.9988	0.9989	0.9989	0.9989	0.9990	0.9990
3.1	0.9990	0.9991	0.9991	0.9991	0.9992	0.9992	0.9992	0.9992	0.9993	0.9993
3.2	0.9993	0.9993	0.9994	0.9994	0.9994	0.9994	0.9994	0.9995	0.9995	0.9995
3.3	0.9995	0.9995	0.9995	0.9996	0.9996	0.9996	0.9996	0.9996	0.9996	0.9997
3.4	0.9997	0.9997	0.9997	0.9997	0.9997	0.9997	0.9997	0.9997	0.9997	0.9998
3.5	0.9998	0.9998	0.9998	0.9998	0.9998	0.9998	0.9998	0.9998	0.9998	0.9998
3.6	0.9998	0.9998	0.9999	0.9999	0.9999	0.9999	0.9999	0.9999	0.9999	0.9999
3.7	0.9999	0.9999	0.9999	0.9999	0.9999	0.9999	0.9999	0.9999	0.9999	0.9999
3.8	0.9999	0.9999	0.9999	0.9999	0.9999	0.9999	0.9999	0.9999	0.9999	0.9999
3.9	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000

PART V

The investigators decided to select two controls for each case from office records of the case-patient's physician. They enrolled a total of 28 cases and 56 controls. Cases and controls were asked about exposures to cooling towers and nearby buildings. Some of these data are displayed in Table 3.

Table 3. Exposures to buildings, Legionnaires' disease outbreak, Louisiana, 1989

	Cases Exposed/Total (%)	Controls Exposed/Total (%)	Odds Ratio	P-value
Indoor exposure to buildings with cooling towers				
Retail Store A	3/28 (11%)	10/54 (19%)	0.5	0.5
Post Office	7/27 (26%)	12/50 (24%)	1.1	0.9
Hospital A	5/28 (18%)	12/54 (22%)	0.8	0.9
Hospital B	3/28 (11%)	7/56 (13%)	0.8	1.0
Paper Mill	2/28 (7%)	4/56 (7%)	1.0	1.0
Outdoor exposure to stores near paper mill cooling towers				
Retail Store A	3/28 (11%)	10/54 (19%)	0.5	0.5
Retail Store B	10/28 (36%)	15/52 (29%)	1.4	0.7
Retail Store D	5/28 (18%)	7/54 (13%)	1.5	0.5
Retail Store E	6/28 (21%)	9/54 (17%)	1.4	0.8
Restaurant A	2/26 (8%)	5/52 (10%)	0.8	1.0
Bank A	11/28 (39%)	19/53 (36%)	1.2	0.9
Butcher Store A	12/27 (44%)	10/54 (19%)	3.5	0.03
Any of the above	19/28 (68%)	33/56 (59%)	1.5	0.6
Outdoor exposure to stores near other large cooling towers				
Drug Store A	7/28 (25%)	15/55 (27%)	0.9	1.0
Drug Store B	13/28 (46%)	20/54 (37%)	1.5	0.6
Doctors Plaza A	2/27 (7%)	8/56 (14%)	0.5	0.5
Retail Store F	4/28 (14%)	6/54 (11%)	1.3	0.7
Exposure to stores frequently reported by case-patients				
Grocery Store A	25/27 (93%)	28/54 (52%)	11.6	<0.01
Grocery Store B	19/28 (68%)	23/54 (43%)	2.9	0.05
Retail Store C	22/28 (79%)	30/54 (56%)	2.9	0.07

Question 15: Interpret these data.

Answer 15
Among the cooling tower exposures, only the butcher store has a substantially elevated odds ratio, but it could account for only 44% of the cases. In contrast, grocery store A has an odds ratio over 11, and could account for almost all of the cases. Grocery store B and retail store C also have elevated odds ratios. It would be interesting to stratify these exposures by grocery store A to see if they hold up.

PART VI

Additional epidemiologic analysis demonstrated a dose-response relationship between time spent in grocery store A and risk of disease. The investigators visited grocery store A and looked for potential sources of aerosolized water. An ultrasonic mist machine was operating over one section of the produce display. No one at grocery store A was familiar with the maintenance or operation of this machine. Permission was obtained to culture a specimen of water from the reservoir of the misting device. The culture from the misting device contained *Legionella pneumophila* serotype 1 (LP-1). Cultures from various cooling towers around town also contain LP-1, but of different subtypes. The investigators were suspicious that this misting device may have been related to the outbreak.

Question 16: Do you think the basic criteria for causation have been satisfied?

Answer 16

Instructor's Note: The point of this question is really whether the association would hold up to scrutiny, whether it meets the criteria for causality. First, generate the list the criteria. Then discuss whether each criterion is met.

Strength of association:	Yes, odds ratio = 11.6 -- this odds ratio is both large and statistically significant and can account for most cases.
Biologic plausibility:	Maybe. Mist machines had never been implicated in a Legionnaires' outbreak before, but isolation of the organism and the machine's aerosol action make it plausible.
Temporality:	Probably. Cases and controls were asked about exposures prior to disease onset; however, we cannot be certain that the mist machine was contaminated at the times of reported exposure.
Dose-response:	Yes.
Consistency:	No. This is a new finding. We are not aware of similar outbreaks associated with mist machines, although mist machines are widely distributed. (However, Legionnaires' disease was known to be associated with aerosolized water sources, so some may consider this consistent.)

On balance, the findings are consistent with the hypotheses of risk of illness being related to exposure to grocery store A and, within grocery store A, to exposure to a contaminated misting device. However, additional studies and steps can be taken to confirm these hypotheses.

Four additional activities were undertaken. A serosurvey was conducted among all grocery store employees in Bogalusa to determine antibody status against LP-1. A second case-control study was undertaken to determine if exposure to the misting device was associated with developing LD. Ten similar misting devices from other parts of the country were cultured. The investigators asked for permission to perform autopsies on two patients who had died of pneumonia early in the epidemic.

Employees at grocery store A were more likely to have elevated antibody titers (≥128) to *Legionella* than employees at the other grocery stores (13/48 versus 7/75, prevalence ratio=2.9, p=0.02.) Analysis of the second case-control study revealed a significant association between disease and purchasing produce which was nearest the mister. Of the 10 mist machines from other parts of the country, 6 grew Legionella. Lung tissue from the two autopsied patients revealed Legionella of the same subtype as that found in grocery store A.

Until now, the news media had not been aware of the outbreak, the investigation, or the results.

Question 17: Who needs to know about these findings? How would you go about reporting the findings?

Answer 17

The primary objective of the investigation was to identify the source and mode of transmission in order to develop appropriate measures to control the outbreak and prevent further cases. Thus, we would want to remove the risk from the mist machines, either by having them cleaned or removed. Since these machines are nationally distributed, cleaning instructions or product recall must also be widely distributed.

We need to inform:

- State health officer and other state and CDC officials, who would not like to be "blind-sided."
- Food and Drug Administration, who can regulate these devices.
- Mist machine manufacturers and grocery industry, who produce and use/maintain these devices. Representatives of these industries may want to meet face-to-face.

Other groups to inform include:

- Townsfolk, through press release, town meeting or press conference.
- Scientific community, through *MMWR*, journal articles, presentations.

PART VII - CONCLUSION

The investigators concluded that the misting device was the source of aerosols that caused the outbreak. They were reluctant to publish the results until the laboratory was able to demonstrate that viable Legionella could be isolated from aerosols produced by the machine. This was expected to take several weeks. In mid-December, the machine was removed from grocery store A and sent to CDC for further study. Since it was apparent that other mist machines were likely to be contaminated with Legionella, the FDA was notified. The FDA developed guidelines for maintaining these mist machines. In early January, the Bogalusa newspaper printed the first article about the outbreak, without knowing its cause. This story was quickly picked up by the New Orleans paper and national news services. Soon, Bogalusa was overrun by reporters wanting to find out the cause of the outbreak. They focused their attention on the paper mill in the center of town, and demanded to know the culture results from the cooling towers.

The LDHH Department issued a press release and a telephone message describing the mist machine findings. Grocery industry officials were notified about the potential problem in trade newspapers and at meetings. The telephone message became public and was widely quoted in newspaper articles.

The type of misting device implicated in the outbreak was new to the grocery industry. These misters produced a visible fog that attracted shoppers, but had no other practical use. They did not help to preserve produce. The health department received reports of similar types of machines used in other settings, such as amusement parks and indoor aquariums. The findings were published in the *MMWR* after laboratory staff were able to isolate Legionella organisms from aerosols produced by the machine.

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